Cytokines

- Small (low molecular weight) proteins that assist in regulating the development of immune effector cell
- Secreted by activated lymphocytes, macrophages (white blood cells and some others)
- Many cytokines exert biological effect by binding to receptors on target cells and triggering signal transduction responses
  - cytokines act locally within a small microenvironment
  - high affinity for receptors ($10^{-10}$ to $10^{-12}$ M)

Action of Cytokines

- The action of cytokines may be
  - autocrine
  - paracrine
  - endocrine
- Cytokines action may be
  - Pleiotropic- any given cytokine may have different biological effect on different target cells
  - Redundant- two or more cytokines that mediate similar functions
  - Synergism- combined effect of two cytokines is greater than the additive effect of each alone
  - Antagonism- the effects of one cytokine inhibit or offset the effects of another
Cytokine Action

- Short lived
- secreted only when cell is activated, not constitutively (like growth factors)
- Most act in an autocrine or paracrine fashion

Function as intercellular messengers:
Should know the following: cytokine, secreted by, target cell, and actions of ......:
- IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-16, IFN-α, β, γ and TGF-β, and TNF-α and β

Cytokine Receptors

- 5 Families of Receptors
  - Immunoglobulin superfamily receptors
  - Class I cytokine receptor family
  - Class II cytokine receptor family
  - Interferon receptor family
  - TNF receptor family
  - Chemokine receptor family

Receptors of different types may have same signal transduction action
**IL-2 Receptor**

- Trimeric receptor composed of α, β, γ chains.
- Occurs in 3 forms that exhibit different affinities for IL-2
  - low affinity monomeric IL-2Rα
  - intermediate affinity dimeric IL-2Rβγ
  - High affinity receptor IL-2Rαβγ
- The α chain is expressed by activated, but not resting, T cells (TAC=T cell activation antigen)
- Signal transduction by IL-2R requires both the β and γ chains, but only the trimeric has high affinity for IL-2

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**IL-2 Receptor**

- The γ chain is constitutively expressed on most lymphoid cells
- The β chain is expressed on most cells constitutively, but is expressed in higher concentration when the cell is activated
- The α chain is expressed only on activated lymphocytes
  - the α receptor- activated CD4+ and CD8+ cells and in low levels on activated B cells
  - the βγ receptor- on NK cells and resting T cells
  - the αβγ receptor- activated CD4+, CD8+ and B cells
Cytokine Antagonists

- Act by binding:
  - directly to a cytokine receptor, but fail to activate cell (competition for receptor)
  - bind directly to cytokine inhibiting its binding
    - *IL-1Ra binds to IL-1 receptor but has no activity (role in regulating inflammatory response)*
  - soluble cytokine receptors (made from enzymatic cleavage of the receptor from the cell membrane) can bind to cytokines
  - some viruses produce cytokine binding proteins (Pox- soluble TNF and IL-1)

T\textsubscript{H}1 and T\textsubscript{H}2 Subset Cytokines

- Cytokine secretion by T\textsubscript{H} subsets help regulate whether the response is humoral or cell mediated
  - Both CD4\textsuperscript{+} and CD8\textsuperscript{+} cells secrete IL-3 and GM-CSF
  - T\textsubscript{H}1 responsible for classical cell-mediated functions (i.e., DTH and activation of T\textsubscript{C} cells, viral cell clearance)
    - *IL-2, IFN-\gamma, TNF-\beta, (GM-CSF and IL-3)*
  - T\textsubscript{H}2 subset responsible as helper for B-cell activation (clears free living bacteria and helminthic parasites, and allergic reactions through IgE class switch by IL-4 and IL-5)
    - *IL-4, IL-5, IL-10, IL-13, (GM-CSF and IL-3)*
**TH1 and TH2 Cell Development**

- IL-4 and IL-12 act on TH cells when TH are activated by antigen:
  - IL-4 cells develop into TH2 subset
  - IL-12 cells develop into TH1 subset
  - These two subsets develop from a common TH0 precursor cell that can secrete IL-2, IL-2 and IFN-γ

- Cytokines secreted by one subset can block the cytokines secreted by the other subset
  - IFN-γ inhibits proliferation of TH2 cells and secretion of IL-10
  - IL-10 down-regulates secretion of IL-2 and IFN-γ

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**TH1 and TH2 Cell Development**

- Cytokine Cross-Regulation
  - IFN-γ and IL-2 (secreted by TH1 subset) promote IgG2a production by B cells but inhibit IgG1 and IgE production
  - IL-4 (secreted by TH2 cells) promotes production of IgG1 and IgE and suppresses production of IgG2a
  - IL-10 does not inhibit TH1 directly but acts on macrophage and interferes with their ability to stimulate TH1 cells

- Progression of some diseases may depend on the balance between TH1 and TH2 subsets
Therapeutic Uses of Cytokines

Purified Cytokines
– regulation of response to alloantigens (organ transplants)
  • try to block activation of $T_H$ and $T_C$ cells to prolong transplants
  • use of IL-1 soluble receptors to block $T_H$ activation
  • Use of anti-TAC antibodies to block IL-2 receptor
  • toxin tagged cytokines (IL-2) to kill $T_H$ cells (only responding cells have IL-2R)
  • Use in LAK cell stimulation
  • Treatment of allergy (block IL-4 using IL-12)